THE RETINA PARTNERS

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Case of the Month – March 2020

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A 55-year-old Filipino male was referred for evaluation of a choroidal neovascular membrane in his left eye. The patient complained of mild, intermittent floaters in both eyes. He denied other ocular or systemic symptoms. On exam, visual acuity was 20/20 in both the right (OD) and left (OS) eyes, intraocular pressures were 23 OD and 24 OS. Anterior segment examination was significant for 1+ nuclear sclerosis in each eye (OU) and trace anterior chamber cell OS; there were no keratic precipitates, nor flare OU. Dilated fundus exam OD conveyed peripapillary atrophy (Figure 1A); in the OS there was a large, mottled-appearing peripapillary choroidal neovascular membrane (Figure 1B).

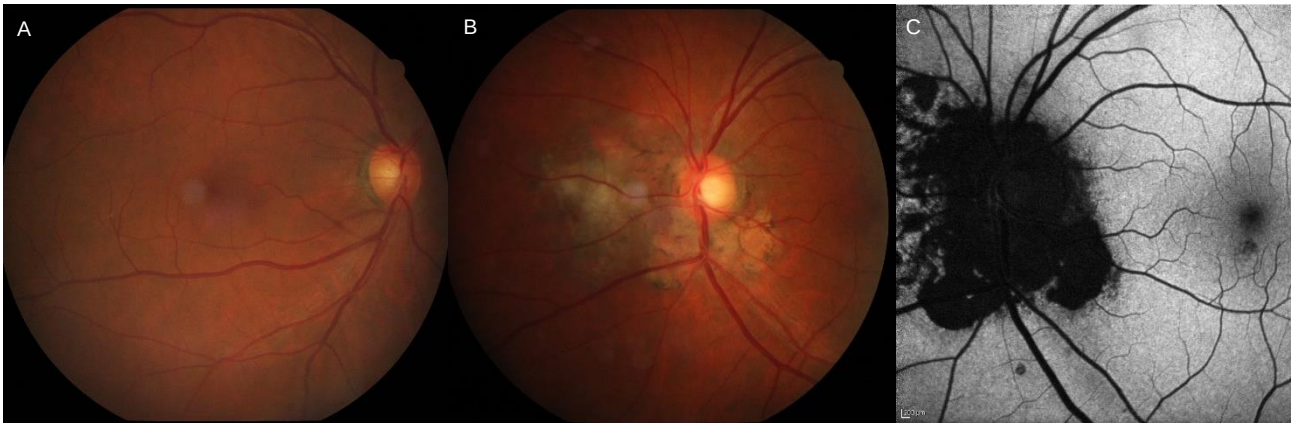

Figure 1: (A) Color fundus photo OD showed peripapillary atrophy. (B) Color fundus photo centered on the optic disc OS revealed a peripapillary choroidal neovascular membrane (CNVM) with a mottled appearance. (C) Autofluorescence OS showed marked hypoautofluorescence corresponding to the peripapillary CNVM.

Fluorescein angiography showed hyperfluorescent peripapillary staining OS>OD (Figure 2A-C) without leakage; there was no evidence of perivascular hyperfluorescence nor signs of posterior inflammation. Indocyanine green angiography showed hypofluorescence of the CNVM OS without choroidal leakage (Figure 2D).

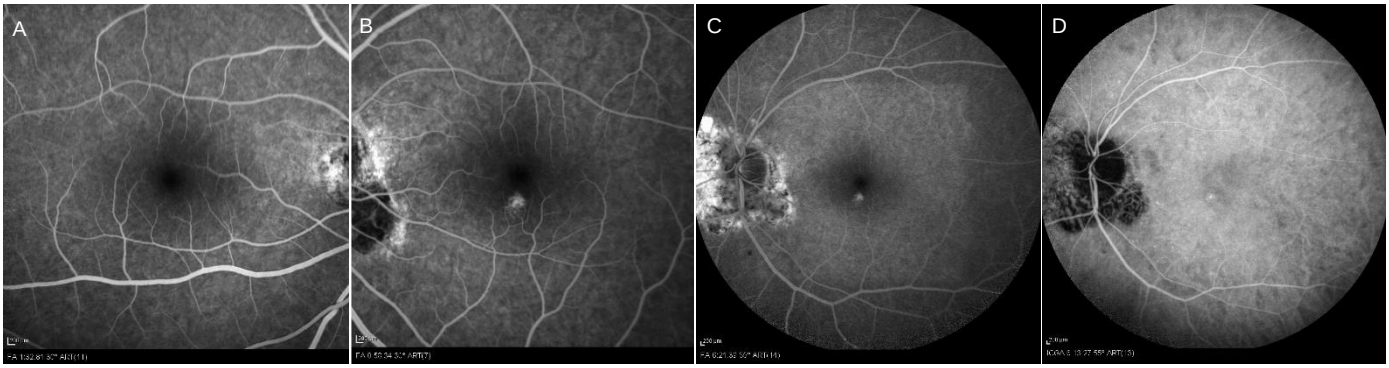

Figure 2: (A) Fluorescein angiography (FA) OD showed peripapillary hyperfluorescent staining. (B-C) FA OS conveyed hyperfluorescent staining of the CNVM without leakage; there was no evidence of vasculitis or posterior inflammation. (D) Indocyanine green angiography revealed hypofluorescent blockage of the CNVM without leakage from the choroid.

Clinical Course:

Based on the findings, a focused workup was pursued, with the anticipation that the most likely diagnosis was an idiopathic, peripapillary choroidal neovascular membrane that could be monitored, given the location and absence of vision complaints. The patient was advised to avoid smoking.

Laboratory workup was significant for a positive QuantiFERON Gold test. Chest X-Rays (CXR; Postero-Anterior & Lateral) were negative. Laboratory workup was otherwise negative (including for HIV and Syphilis). Given the patient's lack of pulmonary or respiratory symptoms, absence of "B symptoms" (e.g. fever, weight loss, night sweats), and negative CXR, a diagnosis of latent tuberculosis was made.

The patient was referred to his Primary Care Physician who referred him to a LA Health Department clinic where he was treated with a 3-month course of daily Isoniazid plus Rifampin. For the trace anterior chamber cell OS, he was treated with topical prednisolone drops, with a slow taper, and quiescence was achieved. At 6-month follow-up, both eyes were quiescent, and there were no changes or growth of the CNVM on exam or testing.

Discussion:

Tuberculosis is a disease caused by respiratory or airborne transmission of the acid-fast bacillus *Mycobacterium tuberculosis*. Active tuberculosis (TB) most commonly affects the lungs, but it can have extrapulmonary manifestations, including intraocular involvement. Approximately 2 billion people worldwide are infected with *M. tuberculosis*, but only about 10% of them have active disease. The prevalence of TB is highest in Southeast Asia, the western Pacific and Africa. In 2004, the Centers for Disease Control and Prevention (CDC) reported 4.9 cases of tuberculosis per 100,000 people. Literature on the rates of ocular involvement report wide ranges, from 1.4 to 18% of patients with TB, depending on the study. Intraocular involvement is thought to develop via hematogenous spread to the eye in most cases.

Tuberculosis can present in a number of ways in the eye. Keratitis, conjunctivitis, and scleritis are rare, but can occur. Most commonly, intraocular TB presents as a posterior uveitis. One longitudinal 10-year study in India reported that 42% of patients presented with posterior uveitis, 36% with anterior uveitis, 11% with panuveitis, and 11% with intermediate uveitis. Intraocular TB may also present as a retinitis, optic neuropathy, or endophthalmitis. Posterior uveitis of TB indicates choroidal involvement. When there is choroidal involvement, it can present in a serpiginous-like fashion, which is thought to occur due to a hypersensitivity reaction to acid-fast bacilli. However, these cases do not respond to immunosuppressive therapy as does serpiginous choroiditis.

Latent tuberculosis infection (LTBI) occurs in people infected with *M. tuberculosis* who have not developed active disease; these patients cannot spread the disease to others. The CDC recommends ruling out active tuberculosis disease prior to initiating treatment for LTBI to avoid the risks of inadequate treatment and development of drug-resistant disease. This differentiation is important because patients with LTBI are not infectious and cannot spread tuberculosis to others; patients with LTBI are typically asymptomatic, have negative Chest X-Rays, and their respiratory specimens are smear and culture negative (see Table 1). The classic screening test is the Tuberculin Skin Test (TST, PPD). The reading and interpretation of TST should be done within 48 to 72 hours of administration. The number of millimeters of induration must be recorded, and the patient stratified according to risk category to determine whether the test is positive or negative.

In many instances, the TST has been replaced by Interferon-Gamma Release Assays (IGRAs), such as the QuantiFERON Gold or T-SPOT TB tests. The advantages of IGRAs are that they require only a single visit for the test, are free of subjective bias in the reading, and are unaffected by a history of the patient having received the Bacillus Calmette–Guérin (BCG) vaccine.

Differentiating Between Latent TB Infection and TB Disease	
LTBI	**TB Disease**
• No symptoms or physical findings suggestive of TB disease. • TST or IGRA result usually positive. • Chest radiograph is typically normal. • If done, respiratory specimens are smear and culture negative. • Cannot spread TB bacteria to others. • Should consider treatment for LTBI to prevent TB disease.	• Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite. • TST or IGRA result usually positive. • Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease. • Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease. • May spread TB bacteria to others. • Needs treatment for TB disease.

Table 1: Differentiating between latent and active TB.

The decision whether to treat LTBI should be made by a physician with expertise in the subject matter, typically an Infectious Disease specialist, or an Internal Medicine specialist working with the local health department to treat this patient population. It is important to consider any underlying risks that the patient may have for converting from LTBI to active tuberculosis. For example, the risk of progression from LTBI to active tuberculosis in healthy persons is about 10% over the course of their lifetime. Meanwhile, the risk of progression from LTBI to active tuberculosis in a patient with human immunodeficiency virus (HIV) infection is about 7 to 10% ***per year***. Indeed, the CDC recommends testing HIV-infected patients for LTBI as soon as they test positive for HIV. In some cases, annual testing is recommended for HIV-Positive patients.

The CDC recommends treating patients with LTBI to prevent them from developing active TB and spreading the disease. In the United States, up to 13 million people may have LTBI. While only 1 in 10 people in the United States with LTBI will progress to active TB, more than 80% of patients who develop active TB progressed to the active state from latent TB infection. The CDC recommends treating patients with a positive IGRA (e.g. QuantiFERON Gold), as well as all patients with a TST (e.g. PPD) reaction of 15 mm or more, or those patients with a TST reaction of 10 mm or more who are also either from high-risk countries where TB is common (including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala), injection drug users, or residents or employees of high-risk facilities (e.g. prisons, nursing homes, homeless shelters, or health care facilities). Patients with a TST reaction of 5 mm or more who are high-risk may also merit treatment – this includes patients with HIV, recent contact with a patient with active TB, fibrotic changes on CXR consistent with previous TB, organ transplant recipients, or patients with immunosuppressed status for other reasons (e.g. >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists, etc).

As of 2018, there are four CDC-recommended treatment regimens for latent TB infection that use isoniazid (INH), rifapentine (RPT), and/or rifampin (RIF). All of the regimens are effective. Healthcare providers should prescribe the more convenient shorter regimens whenever possible, as patients are more likely to complete a shorter treatment regimen. The treatment regimens include:

1. Three months of once-a-week isoniazid plus rifapentine (3HP)
2. Four months of daily rifampin (4R)
3. Three months of daily isoniazid plus rifampin (3HR)
4. Six or nine months of daily isoniazid (6H/9H)

Short-course treatments like 3HP and 4R are effective, safe, and have a higher completion rate than longer 6- to 9-month courses of isoniazid monotherapy (6H/9H). However, if these short-course treatment regimens are not feasible, then 6 months or 9 months of isoniazid monotherapy are acceptable and effective alternatives. All treatment must be modified if the patient has been in contact with an individual with drug-resistant tuberculosis. Clinicians should choose the appropriate treatment regimen based on the susceptibility results of the presumed source case, the patient's comorbid medical conditions, and the potential for drug-drug interactions.

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Take Home Points: Latent Tuberculosis

- Interferon-Gamma Release Assays (QuantiFERON Gold test), are being used more commonly for the screening of tuberculosis and are unaffected by a history of BCG vaccination.
- Latent tuberculosis infection (LTBI) occurs when a patient is infected with *M. tuberculosis* but does not have pulmonary signs and symptoms and cannot spread the disease to others.
- Patients with LTBI should be treated by an expert to reduce their lifetime risk of active TB.


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